Olanzapine-Induced Withdrawal Oculogyric Crisis in an Adolescent With a Neurodevelopmental Disorder

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This case report describes an adolescent female with a complex psychiatric history and Fragile X syndrome who developed an antipsychotic-withdrawal emergent oculogyric crisis (OGC) in approximately 12 hours following reduction in olanzapine dose from 20 mg total daily dose to 5 mg twice daily. The team concluded that the OGC was likely related to olanzapine withdrawal based on the following clinical factors: 1) prior treatment with olanzapine 20 mg for 4 to 5 days/week for several months, without such reaction; 2) proximity of the OGC to the olanzapine dose reduction (within 12 hours); and 3) lack of recurrence with olanzapine dose increase. Additionally, her neurodevelopmental disorder and age were identified as risk factors for an acute dystonic reaction. Published case reports describe withdrawal emergent dystonia, including OGC, following abrupt discontinuation of clozapine in adults. Given structural similarities of clozapine and olanzapine it can be postulated that this phenomenon is based in muscarinic receptor function—specifically, super-sensitized muscarinic receptors may react to excessive acetylcholine upon antipsychotic discontinuation, resulting in muscle motor end plate hyperactivity. Providers caring for pediatric patients with neurodevelopmental disorders should carefully consider risks for withdrawal emergent dystonia, obtain clear medication histories, and consider slow, conservative tapers when discontinuing antipsychotics.

ABBREVIATIONS 5-HT_{1A}, serotonin type 1A; 5-HT_{2A}, serotonin type 2A; D₂, dopamine type 2; D₄, dopamine type 4; EPS, extrapyramidal symptoms; H₁, histamine type 1; IM, intramuscularly; M₁₋₅, muscarinic types 1–5; OGC, oculogyric crisis

KEYWORDS adolescent; adverse drug reaction; antipsychotic drugs; dystonic disorders; eye movements; Fragile X syndrome; olanzapine

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Introduction

Oculogyric crisis (OGC) is a specific type of acute dystonic reaction characterized by paroxysmal, tonic, ocular deviations (usually superiorly or laterally) occurring as a result of sustained contractions of the ocular muscles.¹ Episodes may last minutes to hours, typically warranting emergent intervention. Oculogyric crises have been reported with antipsychotic use, particularly high-potency agents (e.g., haloperidol).² Additionally, published case reports describe withdrawal emergent dystonia and OGC in adult patients following abrupt discontinuation of clozapine.^{3,4} A single case report details OGC occurring in an adult patient following discontinuation of olanzapine.⁵ Our case report describes an adolescent female with a complex psychiatric history and Fragile X syndrome, who developed an OGC within 12 hours of decreasing her olanzapine dose (50% dose reduction). To our knowledge, this is the first available pediatric case reporting OGC as a result of olanzapine tapering.

Case

A 16-year-old (97.5 kg) female with a past psychiatric history significant for an unspecified anxiety disorder,

unspecified disruptive, impulse-control and conduct disorder, mild intellectual disability, and past medical history significant for Fragile X syndrome, was admitted to an inpatient pediatric neuropsychiatric unit with severe aggressive outbursts and homicidal threats toward her mother. On admission, she was taking clonidine immediate release 0.1 mg by mouth every morning and 0.3 mg by mouth at bedtime, duloxetine 60 mg by mouth daily, and olanzapine 20 mg by mouth daily as needed for agitation, although her mother reported that she was administering olanzapine 20 mg by mouth daily 4 to 5 days/week for the past 2 months, given ongoing aggression.

Her psychotropic medication history was extensive, having started psychotropic medications at age 9 years, including multiple trials of stimulants, antidepressants, antipsychotics, and anxiolytics. Notably, she was being treated with aripiprazole 2.5 mg daily at age 9 to 10 years when she experienced her first OGC. Despite experiencing an OGC, she was continued on aripiprazole and titrated to a dose of 5 mg daily. She then experienced another OGC, prompting the team to taper off aripiprazole and initiate risperidone. Upon initiating risperidone 0.5 mg by mouth twice daily, she

was noted by her mother to have 2 OGCs in a 2-week span. Following these initial 2 weeks, she did not have any additional OGCs. The patient continued on risperidone OGC-free for approximately 4 years before the decision was made to discontinue the agent because of significant weight gain. At age 16 years, she was started on olanzapine as needed for agitation.

Given limited evidence that high doses of olanzapine were effective for irritability and aggressive outbursts and the risk for long-term metabolic side effects, the treatment team decided to reduce her olanzapine (Zyprexa, Eli Lilly and Company, Indianapolis, IN) dose to 5 mg by mouth twice daily (an estimated 50% daily dose reduction). Approximately 12 hours following the dose decrease, the patient reported significant ocular pain, discomfort, and inability to control her eye movements. Her eyes were noted to bilaterally deviate upward. Attempts to follow finger tracking resulted in a beating movement, with sustained superior deviation. After further examination with the psychiatrist, nurse, and pharmacist, it was determined that the patient was having an OGC. The patient received diphenhydramine 25 mg by mouth, followed by 25 mg intramuscularly, after which the OGC significantly improved within 30 to 60 minutes. In discussing the OGC with the patient's mother, she again reported that the patient experienced similar events in the past while taking risperidone.

Following the acute dystonic reaction, the treatment team determined that the OGC was induced by rapid antipsychotic withdrawal, given the lack of such adverse effects as an outpatient on much higher sustained doses of olanzapine. The decision was made to increase olanzapine from 5 mg by mouth twice daily to 7.5 mg by mouth twice daily, and further tapering was held for the remainder of her inpatient stay. In addition, benztropine 1 mg by mouth and 1 mg intramuscularly as needed for extrapyramidal symptoms (EPS) were added to her regimen. Benztropine was not administered at the time of the initial acute dystonic reaction, but the as needed oral benztropine was administered 7 hours later for the indication of mild EPS/dystonia symptoms.

During the remainder of this admission, the patient had 2 additional events concerning for OGC, but both were mild in severity compared with the initial crisis. The first was 2 days after her initial crisis, witnessed by the medical team, and appeared to resolve with 1 mg of oral benztropine. The second was 4 days after her initial crisis and was initially witnessed briefly by non-medical treatment staff who alerted the medical team, but it was not appreciated on subsequent physical examination. Following these 2 additional events, benztropine 0.5 mg by mouth was scheduled daily along with an as needed option of benztropine 0.5 mg by mouth or intramuscularly for EPS/dystonia/oculogyric crisis. The patient was discharged home on olanzapine 7.5 mg by mouth twice daily with benztropine 0.5 mg by mouth daily and further tapered to olanzapine 5 mg by mouth

in the morning and 7.5 mg by mouth at bedtime 10 days after discharge. The patient was to follow up with developmental pediatrics to continue this slow taper.

Discussion

Extrapyramidal symptoms, including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia, encompass a broad category of muscular side effects associated with antipsychotic use. First-generation antipsychotics (e.g., haloperidol, fluphenazine) are associated with a significant risk for EPS, given high-potency, postsynaptic dopamine type 2 (D_2) blockade within the nigrostriatal dopamine tract. For this reason, second-generation antipsychotics (e.g., risperidone, aripiprazole) are more commonly prescribed, particularly in pediatric populations.

Acute dystonic reactions are described as acute, painful muscle contractions affecting a variety of muscle groups (e.g., face, eyes, neck, larynx). Oculogyric crisis is a specific type of acute dystonic reaction characterized by paroxysmal, tonic ocular deviations (usually superiorly or laterally) occurring as a result of sustained contractions of the ocular muscles.¹ Episodes may last minutes to hours, typically warranting emergent intervention. Parenteral anticholinergics, including diphenhydramine and benztropine, remain the mainstay of therapy for OGC because of their rapid onset and resolution of distressing symptoms.¹

Risk Factors. Two well-defined risk factors for acute dystonia that were observed in our patient include young age and high dose of antipsychotics. Additional risk factors for acute dystonia include antipsychotic potency, parenteral administration, male sex, non-white ethnicity, and a history of substance use.^{1,6} Adolescents with developmental delay, such as the one described in this case, have been reported to be at increased risk for EPS. In a study evaluating the safety and efficacy of atypical antipsychotics in adolescents with developmental delay, Friedlander et al⁷ concluded that atypical antipsychotics are useful in treating various psychiatric conditions associated with the following developmental delays: cerebral palsy, Down syndrome, fetal alcohol effect, Rubella syndrome, Sotos syndrome, velocardiofacial syndrome, Noonan syndrome, and tuberous sclerosis. The most common adverse events to occur with risperidone in this patient population ($n = 40$) were rigidity or tremor in 12.5% of patients, followed by OGC occurring in 5% of patients. Additionally, 15% of patients experienced lethargy and 12.5% experienced weight gain. In patients administered olanzapine ($n = 14$), 21% experienced EPS, with 2 of these patients experiencing OGC. Interestingly, all 17 patients on risperidone or olanzapine who experienced dystonias and dyskinesias were adolescent females.⁷

Withdrawal Emergent OGC. Acute dystonic reactions and dyskinesias have been reported in conjunction with not only antipsychotic use, but also

rapid antipsychotic withdrawal.⁶ Pediatric patients with neurodevelopmental disorders appear to be particularly sensitive to these effects, warranting close consideration for slower antipsychotic tapers. Our patient experienced OGC approximately 12 hours following a reduction in olanzapine dose. Other reports of withdrawal OGC have most commonly been reported following rapid clozapine discontinuation or taper, and less commonly following olanzapine discontinuation or taper.^{3–5} Karaş et al⁵ described withdrawal emergent dyskinesia and supersensitivity in a 59-year-old man after self-discontinuing olanzapine (10 mg/day) following 2 years of treatment on this dosage. Following olanzapine discontinuation, he acutely experienced fears of being followed and hurt, insomnia, and involuntary chewing, and lip smacking, which previously were not present. Olanzapine was reinitiated, and symptoms subsided within 1 week.

Sarma et al³ described a case of clozapine withdrawal emergent dystonia, OGC, and rebound psychosis in an adult woman. Clozapine 400 mg daily was abruptly discontinued given alteration in consciousness, elevated temperature, and concern for bowel impaction. Five days following clozapine discontinuation, the patient developed 3 distinct, acute OGCs, each lasting 60 to 90 minutes, within a 24-hour period. Following administration of promethazine 50 mg IM, the dystonia resolved within minutes. The treatment team determined that this was a clozapine withdrawal OGC and made the decision to restart clozapine; since its re-initiation no recurrence of dystonia has been noted.

Mendhekar et al⁴ described an OGC in an 18-year-old woman with intellectual disability; the OGC occurred within 48 hours of discontinuing clozapine 300 mg QHS (which she had been taking for <1 month). The acute OGC was described as “uprolling of the eyes” lasting for 60 to 90 minutes and recurring every 2 to 4 hours. Upon clozapine re-initiation her symptoms immediately resolved. To our knowledge, our patient appears to be the only published case of olanzapine-associated withdrawal dystonia in a pediatric patient. This patient represents a unique diagnostic profile, including Fragile X syndrome and intellectual disability. Our patient received a diagnosis of Fragile X syndrome at the age of 3 years, which is the most common inherited cause of developmental delay in children. Fragile X syndrome is often associated with social anxiety, depression, impulse control disorder, and mood disorders requiring pharmacotherapy.⁸ Despite having a neurodevelopmental diagnosis, her expressive communication skills were a personal strength. The patient was concrete in her thought process but able to alert staff that she was in distress and pain, and that she could not control her eye movements. On examination, she was able to follow directions and exhibit deficits in her extraocular movement control. Based on these clinical findings, OGC was determined to be the most likely causative factor.

Mechanism of Action for Withdrawal Emergent OGC. To understand the mechanism by which olanzapine and clozapine discontinuation may result in withdrawal OGC, it is important to consider their pharmacologic similarities and differences. Olanzapine and clozapine have similar chemical structures with complex binding patterns in comparison with other atypical antipsychotics.

Clozapine, a dibenzodiazepine, and olanzapine, a thienobenzodiazepine, are potent serotonin type 2A (5-HT_{2A}) antagonists in addition to being potent antagonists at histamine type 1 (H₁), α-1 adrenergic, and muscarinic types 1 to 5 (M_{1–5}) receptors, the latter 3 conferring risk for sedation, orthostatic vital sign changes, drying, and metabolic adverse effects. Clozapine is unique among antipsychotics, given its high affinity for dopamine type 4 (D₄) receptors and minimal affinity to D₂ receptors, conferring minimal risk for EPS. Similarly, olanzapine has higher affinity for H₁, 5-HT_{2A}, D₄, M₄, and M₁ than it does for D₂.^{9,10} It has been well described that D₂ blockade within the nigrostriatal dopamine track plays a critical role in the development of EPS, whereas 5-HT_{2A} antagonism in cortical pyramidal neurons may play a protective role through glutamatergic regulation of downstream dopamine release. For this reason, second-generation antipsychotics are known to have a lower risk for EPS compared with first-generation antipsychotics. Additionally, low incidence of EPS has been associated with atypical antipsychotics with a high affinity as antagonists for 5-HT_{1A} and muscarinic cholinergic receptors. Among second-generation antipsychotics, risperidone is thought to have the highest risk for EPS given its potent D₂ binding affinity, followed by paliperidone, lurasidone, and asenapine. Olanzapine, in comparison with these atypical antipsychotics, generally has a low risk of EPS even at higher doses (>15 mg/day).¹¹ What is less well described is the mechanism by which these agents may cause withdrawal dystonia—particularly given their reduced affinity to postsynaptic D₂ receptors. Acetylcholine, an excitatory neurotransmitter within the basal ganglia, binds M₁ and M₂ receptors and indirectly to nicotinic acetylcholine receptors to excite motor end plates. As potent antagonists of muscarinic M_{1–5} acetylcholine receptors, it can be postulated that with chronic olanzapine or clozapine treatment these receptors become upregulated and super-sensitized within the basal ganglia. Upon rapid withdrawal of olanzapine or clozapine, the super-sensitized receptors react excessively to acetylcholine, with resultant muscle motor end plate hyperactivity (e.g., dystonia).³ In line with this hypothesis, re-initiation of the antipsychotic or administration of a potent anticholinergic (e.g., diphenhydramine or benztropine) should resolve the acute and painful muscle symptoms.

Limitation of Our Report. The treatment team's determination that the OGC was related to olanzapine withdrawal was made based on consideration for the

following clinical factors: 1) prior treatment with olanzapine 20 mg 4 to 5 days/week for several months, without such reaction; 2) proximity of the OGC to the olanzapine dose reduction (within 12 hours); and 3) lack of recurrence with olanzapine dose increase. Additionally, the patient's neurodevelopmental disorder and age were identified as risk factors for an acute dystonic reaction.

Notably, symptoms did improve with an olanzapine dose increase, although they did not completely resolve. Two additional OGCs were described during the remainder of her admission: one resolved quickly with benztropine administration and the other was determined to be a questionable OGC on exam by the treatment team. On discharge, the plan was to continue to slowly taper off olanzapine.

Conclusion

Given the lack of studies and publications highlighting the risk for antipsychotic withdrawal dystonic reactions in the pediatric neurodevelopmental population, our team felt it was important to add this case report to the body of scientific literature. Special consideration should be given not only to the initiation but also to the discontinuation of antipsychotics in pediatric patients with neurodevelopmental diagnoses. We highly recommend obtaining a detailed medication history during the lifetime of the patient, including history of patient and caregiver administration compliance, when considering taper antipsychotics. If a patient is considered at increased risk for developing a dystonic reaction, providers should consider a slow taper ($\leq 25\%$ dose decrease every 5 to 7 days) and conservative dosing to achieve medication discontinuation. Providers may also wish to consider the addition of prophylaxis (i.e., benztropine or diphenhydramine) while antipsychotics are being tapered and discontinued in high-risk cases.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, institution review board/ethics committee review and informed consent were not required.

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